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Original Articles, Selections and Translations.

ART. I.—SAPONIN IN ITS RELATIONS TO PHYSIOLOGY.

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(*Continued from page* 291.)

GENERAL ACTION.

UNDER this head will be studied the action of the drug when introduced by absorption, and when it is injected into the blood-vessel system.

ACTION ON THE NERVOUS SYSTEM.

The peripheral *afferent* and *efferent nerves* remain unaffected when saponin is introduced into the veins of the general circulation. The excitability of the nerves for electrical irritants remains unaffected under these circumstances. When introduced into an artery, such as the femoral, the nerves of the part of the body into which the drug was injected are first excited and then paralyzed by the drug. The other nerves of the body retaining their functions for a long period thereafter, proves, as was before stated, that this effect is due to the local action of the drug.

On the *spinal cord* the drug has a more decided action. After the destruction of the brains of frogs it is well known that spinal reflexes become more marked. When, however, frogs thus prepared are poisoned with saponin, a gradual abolition of reflex action occurs. This was determined by the use of a solution of acetic acid which was just sufficient in the normal animal to produce reflex movements when applied to the web of the feet. About a half hour after the poisoning the solution of the acid previously employed had to be increased in strength in order to produce reflex movements. After a varying period—usually about an hour—it was found that application of strong sulphuric acid failed to produce these movements.

The same results, less perfectly, it is true, were obtained in dogs, rabbits, and cats in whom section of the pons had been made, at its junction with the medulla oblongata. Saponin therefore produces abolition of the reflex activity of the spinal cord. This paralysis is not due to any action on the motor nerves, as these respond to irritants for some time after the cessation of reflex movements.

The general action of saponin on the *brain* is very interesting, as it appears to be a sleep-producing agent. .02–.1 gram. of the drug injected into a mesenteric or femoral vein of a cat produces deep sleep in 15–25 minutes, from which the animal can be aroused, to fall again into the same somnolent state when the excitation is removed. If the dose be very large the animal gradually loses all sensibility and falls into a state of coma, from which it cannot be aroused, and dies in about two hours. If a smaller dose be given a cat or a dog this state of insensibility lasts several hours, when the animal gradually recovers without any untoward symptoms. An injection of .002 into the back of a mouse, pigeon, or sparrow, also produces this sleep, accompanied by loss of sensibility and followed by coma and death.

Accompanying and preceding this somnolent state in mammals, and replacing it in frogs, there is complete abolition of all the so-called voluntary movements. "Saponized" frogs when placed on their backs make no attempt to re-attain the abdominal position, though at the time the reflex activity may

be unaffected, showing that either the animal is unaware of its position, owing to an action of the drug on the perceiving organs of the central nervous system; or that there is paresis of the peripheral sensory or motor nerves. As reflex movements can still be excited the latter cannot be the cause.

Saponin therefore *produces sleep by greatly reducing or even abolishing the perceptive faculties of animals.*

When introduced into the general circulation of mammals and frogs, saponin exerts no influence whatsoever on the functions of the *muscles.*

ACTION ON THE CIRCULATORY SYSTEM.

On the blood-pressure in the Arteries.—Hoppe* saw a weak solution of saponin first excite and then depress the actions of the heart.

Köhler† found in rabbits and dogs, that after an evanescent rise the blood-pressure always diminishes, and believes this to be due to excitation, followed by paralysis, of the vasomotor "centres." He further says that in the "saponized" animal the heart is cut off from all nervous influences except those exerted by its own intrinsic gangliæ.

For reasons which will be apparent I will divide my experiments on the circulatory action of saponin into the following three classes:

1. The action of saponin on the arterial pressure when injected into a jugular vein;

2. The action of saponin on the arterial pressure when injected into a femoral vein;

3. The action of saponin on the arterial pressure when introduced into an efferent blood-vessel.

Saponin injected into a jugular vein.—Owing to the heart-nerves and blood-vessels varying in the different species of mammals, I have endeavored to separate the experiments on the different animals as much as possible, and at the same time to keep up a comparison between them. In the first series of experiments the only operations were the insertion

* "Die Nervenwirkung d. Arzneimittel," Hft. IV., p. 137.

† *Arch. f. exp. Path.*, I., p. 138-162. "Die locale Anæsthesir. d. Saponin," p. 78. *Physiologischen Therapeutik*, 1876, p. 286.

of a canula, which was connected with a manometer,* into the common carotid or femoral arteries, and then placing a canula into the external jugular vein through which the solution of the drug was injected towards the heart.

Following such an injection in rabbits I never saw a rise but always a very decided fall in the arterial pressure, as will be illustrated in the following experiments:

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
1.	Albino Rabbit.	Oct. 4, 1877.		Canula in carotid artery.
		9.34.	71.9 mm.	
		.10	71.9 "	
		.20	71.9 "	
		.30	71.9 "	
		.40	71.8 "	
		.50		Injected .05 gram. into external jugular vein towards the heart.
		.53	71.9 "	
		9.35.	66.3 "	
		.10	40.9 "	
		.20	40.7 "	
		.40	46.3 "	
		.50	54.9 "	
		9.36.	55.7 "	Animal died about this time.

In the cat the fall in the blood-pressure produced by the injection of saponin into the jugular vein is followed by a secondary rise, so that the pressure resulting may greatly exceed the normal arterial pressure.

* This consisted of a U-shaped tube containing mercury. On this mercury was placed a swimmer of hard rubber and attached to this was a wire which wrote the variations of pressure on a revolving drum previously sooted with lamp-black.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
3.	Cat.	Nov. 4, 1877.		Canula in carotid artery.
		3.21.	99.4 mm.	
		.10	99.4 "	
		.20		Injected .037 gram. into external jugular vein towards the heart.
		.30	99.4 "	
		.40	96. "	
		.50	89.7 "	
		3.22.	87.5 "	
		.10	89.1 "	
		.20	92.2 "	
		.30	95.1 "	
		.40	97.9 "	
		.50	99.4 "	
		3.23.10	108.4 "	

When, however, a very large dose of the drug was injected into the jugular vein of a cat this secondary rise in arterial pressure did not occur.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
4.	Cat.	Dec. 5, 1877.		Canula in carotid.
		1 sec.	83.9 mm.	
		5 "		Injected .2 gram. into external jugular vein towards the heart.
		10 "	78.4 "	
		20 "	76.8 "	
		30 "	76.1 "	
		40 "	57.4 "	
		60 "	28.7 "	
		100 "	00. "	The animal is dead.

In the dog the same decided fall in pressure is observed to follow the introduction of a large dose of saponin into the jugular vein. This is however always followed by a secondary rise in the arterial pressure.

To what is the fall in the arterial pressure due? A diminished blood-pressure may be due: first, to a paralysis of the vaso-motor "centres" allowing a large quantity of blood to accumulate in the capillaries; second, it may be due to an active dilatation of the walls of the blood-vessels through the agency of the vaso-dilator nerves; third, to irritation of the vagus centres, trunks, or peripheral extremities; fourth, to a contraction of the pulmonary blood-vessels preventing the ærated blood from having free access to the arterial heart; fifth, to a paralysis of the heart itself.

It was first shown by Stilling* and Henle,† that certain nerves have for their function the contracting of the walls of the blood-vessels. To these the name of vaso-motors and vaso-constrictors has been bestowed. In 1859, Schiff,‡ and in 1871, Owsjannikow§ experimentally demonstrated that these nerves were under the control of a "centre" situated in the medulla oblongata, to which the name of "vaso-motor centre" was given. It is now well known to physiologists that irritation of a sensory nerve frequently‖ produces, through reflex stimulation of this "centre," a decided rise in the blood-pressure. This rise is by no means certain to occur if the pneumogastrics remain intact, as under these circumstances I have observed that irritation of the anterior crural nerve produces a very decided fall in the pressure, which was replaced by a rise when the pneumogastrics were cut or their inhibitory fibres paralyzed by atropine.

It was therefore necessary in the experiments on saponin to first cut the pneumogastric nerves; then to irritate the ante-

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* *Unters. u. d. Spinal-Irritation*, Leipzic, 1840, p. 163.

† *Path. Untersuch.*, Berlin, 1840, p. 105.

‡ *Unters. z. Physiol. d. Nervensystems*, Frankfort, 1855, p. 219.

§ *Ludwig's Arbeiten a. d. phys. Laborat.*, Leipzic, VI., p. 21.

‖ After curarization the rise in the blood-pressure from irritation is almost constant.

rior crural, and observe the rise in the pressure produced in the manometer connected with the carotid or femoral arteries of the animal experimented upon. The drug being now given it was possible to determine if the vaso-motor "centre" was affected, by observing whether or not the irritation of a sensory nerve still produced an increased blood-pressure.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
6.	Dog.	Dec. 17, 1877.		Canula in carotid. Pneumogastrics cut.
		1 sec.	121.5 mm.	
		5 "		Injected .3 gram. into internal jugular vein.
		10 "	113.7 "	
		20 "	104.3 "	
		22 "		Irritation of anterior crural nerve.
		23 "	130.9 "	
		25 "	138.7 "	Cessation of the irritation.
		27 "	105.1 "	
7.	Cat.	Dec. 17, 1877		Canula in carotid artery. Pneumogastrics cut.
		1 sec.	80.6 mm.	
		5 "		Injected .25 gram. into internal jugular vein.
		10 "	62. "	
		12 "		Irritation of anterior crural nerve.
		13 "	67.5 "	
		17 "	74.7 "	
		20 "	79.2 "	
		21 "		Cessation of irritation.
		24 "	58.8 "	

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
8.	Albino Rabbit.	Oct. 8, 1877.		Canula in carotid. Pneumogastrics cut. Injected .015 gram. into external jugular vein.
		1 sec.	78.1 mm.	
		5 "		Irritated sciatic nerve.
		7 "	100. "	
		15 "	109.2 "	
		20 "	113.8 "	
		21 "		Cessation of irritation.
		23 "	54.8 "	

It will be observed in the foregoing experiments that irritation of a sensory nerve still produces a rise in the pressure even if very large doses of saponin have been given. The cause of the diminished blood-pressure is therefore not to be sought for in a paralysis of the vaso-motor "centre" or nerves, as no such paralysis exists in animals poisoned by saponin.

The same result was arrived at through the following experiments where the greater portion of the vaso-motor nerves were cut, through high section of the spinal cord, after which operation saponin produced a fall in the pressure.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
9.	Cat.	Dec. 10, 1877.		Canula in carotid. Cord cut at fifth cervical vertebra.
		1 sec.	98.4 mm.	
		4 "		.1 gram. into external jugular vein.
		10 "	97.8 "	
		15 "	87.2 "	
		20 "	87.2 "	
		25 "	93.1 "	
		30 "	96.3 "	
		35 "	98.4 "	
		40 "	98.4 "	
		120 "	98.4 "	

No. of Experiment.	Amount.	Time.	Pressure.	REMARKS.
11.	Dog.	Dec. 6, 1877.		Canula in carotid. Cord cut at fifth cervical vertebra.
		1 sec.	137. mm.	
		6 "		.3 gram. into internal jugular vein.
		10 "	137. "	
		12 "	133.2 "	
		15 "	131.1 "	
		20 "	131. "	
		30 "	129.5 "	
		40 "	121.6 "	
		50 "	128.7 "	
		55 "	135.6 "	
		60 "	137. "	
		120 "	137. "	

The experiments of various physiologists, and especially those of Schiff* and Goltz,† have taught us that, while there are vaso-constrictors, there are also vaso-dilating nerves. Comparatively little is known of these, and, by some physiologists, their existence is still doubted. Consequently it is difficult at the present time to determine whether or not the fall in the blood-pressure is caused by their being irritated by saponin. All that I have been able to do thus far to determine if the fall in the blood-pressure following an injection of this drug into the jugular vein is due to such an irritation, has yielded negative results. If such an active dilatation of the capillaries takes place it must be observable in the vessels in the web of the frog's foot, but, so far as my observations have gone, no such effect ever followed the injection of the drug into the lymph sacs of this animal. On the contrary the size of the capillaries diminishes.

* *Mitth. d. naturforsch. Gesellsch. in Bern*, 1856. *Oversigt over det kgl. danske Vidensk. Selsk. Forhandlunger*, 1857, Nr. 8. *Comptes Rendus*, 1862, II., p. 540, etc.

† *Arch. f. d. ges. Physiologie*, IX., p. 174, 197. 1874.

Were the diminished arterial pressure due to irritation of the pneumogastric centres or trunk, it would cease to occur when the connections of this nerve with the heart are destroyed. This was done in a number of experiments by cutting the neck pneumogastrics. If now on injecting saponin, the pressure still diminished, it would be conclusive proof that irritation of these structures was not the cause of the fall.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
12.	Albino Rabbit.	Nov. 15, 1877.		Canula in carotid artery. Pneumogastrics cut.
		12.04_	61_1 mm.	
		_10		.015 gram. into external jugular vein towards the heart.
		_20	59_5 "	
		_30	34_3 "	
		_40	31_1 "	
		_50	37_7 "	
		12_06	59_4 "	Animal died some hours later.

As the fall of pressure, in these and in a large number of similar experiments on rabbits, still occurred even when the pneumogastrics were cut, it should perhaps be concluded that this fall was independent of any action on these nerves. But before doing this it will be well to see whether the same holds good in dogs and cats.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
15.	Large Cat.	Dec. 3, 1877.		Canula in carotid. Vagi cut.
		1 sec.	102_6 mm.	
		7 "		.023 gram. into external jugular vein.
		9 "	93_2 "	
		12 "	92_1 "	
		15 "	81_6 "	
		25 "	60_4 "	
		30 "	67_6 "	
		40 "	79_5 "	
		45 "	86_4 "	Animal recovered.

From these experiments it appears that the pneumogastrics have nothing to do with the fall in blood-pressure in cats.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
16.	Small Dog.	Nov. 13, 1877.		Canula in carotid. Vagi cut in neck.
		12.44.	95. mm.	
		.10		Injected .16 gram. into jugular vein towards the heart.
		.20	95. "	
		.30	104.1 "	
		12.45	95.2 "	
		.10	100.4 "	
		12.46.20	103.3 "	Animal recovered.
17.	Hound.	Nov. 22, 1877.		Canula in carotid. Vagi cut.
		1 sec.	138.8 mm.	
		3 "		Injected .25 gram. into external jugular vein towards the heart.
		4 "	139.3 "	
		11 "	149.2 "	
		15 "	152. "	
		24 "	144.9 "	
		60 "	137. "	Animal recovered.

From these last experiments on dogs we arrive at a conclusion which is apparently at variance with the results obtained in rabbits and cats. Why is it that in rabbits and cats, the blood-pressure is still diminished by the drug when the vagi are cut, yet in dogs a rise in the pressure occurs under the same circumstances? It may be due to an anatomical difference in the distribution of the pneumogastric fibres in different animals. In the cat and rabbit, as was shown by Ludwig

and Cyon,* and others, there is a little nerve lying close to the main vagus trunk in the neck, of which it is a branch, which has the function of a true circulatory depressor; *i. e.*, when this nerve is cut and its central end irritated, the pressure descends though the frequency of the pulse remains unaffected.† In the dog this little nerve is included in the main vagus trunk, and when the latter is cut the depressor nerve is also cut. In the rabbit, and frequently in the cat, when the vagi trunks are cut the depressors escape. It was therefore necessary to determine if the same rise in pressure as is produced in dogs by saponin, after the vagi trunks have been cut, occurs also in cats and rabbits when the depressors were cut with the vagi trunks.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
18.	Rabbit.	Nov. 19, 1877.		Canula in carotid. Vagi and depressors cut.
		1 sec.	86.1 mm.	
		5 "	85.9 "	
		10 "		Injected .062 gram. into jugular vein.
		11 "	84.2 "	
		13 "	69.6 "	
		17 "	64.8 "	
		20 "	62. "	In three minutes the animal was dead.
20.	Large Cat.	Dec. 3, 1877.		Canula in carotid. Vagi and depressors cut.
		1 sec.	111.6 mm.	
		4 "		
		7 "	103.9 "	.03 gram. into external jugular vein.
		12 "	98.4 "	
		16 "	92.5 "	
		17 "	108.2 "	
		20 "	112.7 "	
		24 "	118.5 "	
		26 "	122. "	
		40 "	120.9 "	

* *Bericht d. Sächs. Gesellsch.*, 1866.

† To prevent reflex inhibition of heart's movements in these experiments the vagi nerves must previously be cut.

The depressor nerves being cut in these animals and saponin still producing a diminished blood-pressure, some other cause must be sought to explain the rise in pressure following the injection of the drug into the jugular veins of dogs in whom the pneumogastrics have been cut.

On referring to the experiments on dogs, where a fall in the blood-pressure occurred, it will be observed that the solution of saponin was introduced into the internal jugular vein. In order to keep the injecting canula in the vein, a canula over four inches long was used, while in the experiments where the pneumogastrics were cut, the drug was injected by means of an ordinary hypodermic needle tied into the external jugular vein. By the former mode of introduction we have the direct action of the drug on the heart, which produces the lowering in the pressure, while by the latter method the drug only reaches the heart muscle after being diluted with the blood coming from other portions of the body. That this explanation is the correct one will be seen in the following experiments on dogs, where, after the pneumogastrics were cut, and saponin injected into the heart, a fall instead of a rise in blood-pressure was produced.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
22.	Large Dog.	Nov. 18, 1877.		Canula in carotid. Vagi cut. A 4 in. long injecting canula introduced into the internal jugular vein towards the heart.
		1 sec.	90. mm.	
		3 "		.125 gram. into heart.
		5 "	84.4 "	
		11 "	80.7 "	
		40 "	75. "	
		2 min.	91. "	
24.	Small Dog.	Dec. 8, 1877.		Canula in femoral artery.
		1 sec.	96.4 mm.	
		3 "		.1 gram. into heart.
		10 "	86.2 "	
		15 "	81.3 "	
		20 "	79.8 "	
		25 "	85.2 "	
		30 "	86.7 "	
		40 "	97.6 "	

The reason why an injection of saponin into the external jugular vein of rabbits and cats produces a fall becomes apparent after these experiments. In these smaller animals, owing to the shortness of the distance from the point of injection to the heart, comparatively little dilution of the injected material occurs, before its effects on the heart become manifest, and the same result is obtained as from an injection directly into the hearts of dogs. When, however, saponin is injected peripherally into the external jugular vein in the smaller animals, similar phenomena to those which follow an injection into the external jugular of dogs occur.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
25.	Rabbit.	Nov. 19, 1877.		Canula in carotid.
		1 sec.	75.7 mm.	
		6 "	75.7 "	
		10 "		Injected .02 gram. into external jugular vein towards the periphery.
		12 "	75.7 "	
		14 "	78. "	
		16 "	79.5 "	
		17 "	81.4 "	
		20 "	80.2 "	
		24 "	79. "	
		60 "	59.7 "	

These experiments lead naturally to the conclusion that the fall in blood-pressure following an injection of saponin into the jugular vein is due to the direct action of the drug on the heart. What is the nature of this action? Is it on the nerves or ganglia, or on the muscular tissue?

That the fall in blood-pressure is not due to any action on the heart nerves is shown by the circumstance that a "saponized" heart will contract when mechanically irritated. Besides this, in about two-thirds of the experiments, this muscle

continued to contract "automatically" for a long time after the respirations had ceased; but, though the left ventricle was filled with liquid blood, none of it was expelled into the aorta by these contractions. On closer examination it was observed that while the external muscular fibres of the heart still continued to contract, the internal fibres were absolutely motionless. Microscopically examined, the internal muscular fibres were found to have lost their striations and to present changes like those previously described as being produced by the local action of saponin on the skeleton muscles. In the experiments where the drug produced death in a few seconds these changes were best marked, and the hearts of these animals could no longer be brought to contract by irritation.

The rise in the arterial pressure succeeding the fall will be treated of later.

Action of saponin on the blood-pressure when injected into a femoral vein.—Experiments on rabbits. The first thing noticeable in these experiments is that doses which were immediately fatal when introduced into the jugular vein could be injected with impunity into the femoral vein. This is another argument in favor of the view before expressed: that, by the former method of injection, direct paralysis of the heart is produced. The arterial pressure is augmented by the latter method of introduction.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
28.	Albino Rabbit.	Dec. 14, 1877.		Canula in carotid.
		1 sec.	87.3 mm.	
		5 "		.035 gram. into femoral vein.
		7 "	87.6 "	
		15 "	88.1 "	
		30 "	88.1 "	
		50 "	89.6 "	
		60 "	89.7 "	
		70 "	89.9 "	
		75 "	88.4 "	
		90 "	87.6 "	
		120 "	82.1 "	

The same augmentation in the blood-pressure was observed in the experiments on cats and dogs.

The arterial pressure can be augmented by a drug :

1. By paralysis of the vagus roots, trunks or terminal heart fibres;
2. By stimulation of the afferent (sympathetic) circulatory fibres;
3. By stimulation of the vaso-motor centres or fibres;
4. By direct irritation of the walls of the blood-vessels.

Is the increased blood-pressure due to paralysis of the vagus? From the experiments which I made to determine the action of saponin on the cardio-inhibitory nerves, it appeared at first as if this was the true explanation of the augmented pressure. To determine this more certainly, I cut the pneumogastrics in a number of animals, and then observed the blood-pressure after an injection of the drug into the femoral vein.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
32.	Rabbit.	Dec. 11, 1877.		Canula in carotid. Vagi cut.
		1 sec.	57.4 mm.	
		5 "		.015 gram. into femoral vein.
		13 "	59.8 "	
		20 "	59. "	
		30 "	59.6 "	
		40 "	59.2 "	
		50 "	59.6 "	
		60 "	61.4 "	
		65 "	61.7 "	
		120 "	57.4 "	
34.	Dog.	Nov. 13, 1877.		Canula in carotid. Vagi cut.
		3 09	123.1 mm.	.15 gram. into femoral vein.
		.10	131.4 "	
		.20	125. "	
		.30	124.7 "	
		.40	128.9 "	
		.60	127.8 "	

On referring back to experiments 17 and 20 it will be seen that a rise in the blood-pressure can follow an injection into the jugular vein, notwithstanding the previous section of the pneumogastrics. As, following the injection into a femoral vein, an augmentation in the arterial pressure is produced even after the previous section of the vagi, it is conclusively demonstrated that the rise in pressure is not due to their paralysis.

To determine whether this augmentation is due to stimulation of the vaso-motor "centre," I cut the spinal cord in rabbits, cats and dogs, at the fifth cervical vertebra,* in order to cut the larger number of the vaso-motor nerves, and then introduced saponin into the femoral vein. Under these circumstances the blood-pressure never rose.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
35.	Albino Rabbit.	Dec. 20, 1877.		Canula in carotid. Spinal cord cut at lower edge of fifth cervical vertebra.
		1 sec.	76.7 mm.	
		3 "		.035 gram. into femoral vein.
		10 "	75.8 "	
		20 "	71.6 "	
		30 "	69.5 "	
		40 "	66.1 "	
		60 "	63.6 "	
37.	Large Dog.	Dec. 12, 1877.		Canula in carotid. Medulla oblongata destroyed. Artificial respiration.
		1 sec.	122.to 122.5 mm	
		5 "		.1 gram. into femoral vein.
		10 "	122.to 122.5 "	
		15 "	122.to 122.5 "	
		20 "	122.to 122.5 "	
		40 "	122.to 122.5 "	
		60 "	122.to 122.5 "	
		120 "	122.to 122.5 "	In ten minutes the pressure was still the same.

* That is, above the origin of the splanchnics.

It was found in a large number of experiments similar to the above, that the rise in pressure never occurred when the medulla oblongata was destroyed at the calamus, and that it was reduced to a minimum by section of the spinal cord in the neck. By the former of these methods all the vaso-motor fibres were destroyed excepting those which directly supply *some* of the blood-vessels of the brain;* while, by the latter, the greater part, though not all, of these nerves were rendered functionless. The secondary rise in pressure following the fall produced by an injection of saponin directly into the heart also ceases to occur after section of the spinal cord in the neck.

The cause of the augmentation in the blood-pressure following the introduction of saponin must therefore be stimulation of the vaso-motor "centre." Whether this stimulation is directly produced by the action of the drug on the "centre," or whether it occurs reflexly from irritation of sensory nerves, will be discussed later.

When a large dose of saponin is injected into the femoral vein, the same palsy of the heart is produced as follows the injection of a much smaller dose into the jugular vein.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
43.	Small Rabbit.	Dec. 24, 1877.		Canula in carotid. Vagi cut.
		1 sec.	67.3 mm.	
		3 "		.05 gram. into femoral vein.
		7 "	48.9 "	
		10 "	23.6 "	
		15 "	Negative.	Animal dead.
44.	Cat.	Dec. 21, 1877		Canula in carotid.
		1 sec.	102.7 mm.	
		5 "		.15 gram. into femoral vein.
		10 "	73.4 "	
		15 "	46.5 "	
		25 "	Negative.	Animal dead.

* That nerves (vaso-motor?) proceed from cerebral cells to the coats of the blood-vessels I have often observed.

This fall in the pressure, immediately following the injection of a large dose of the glucoside into the femoral vein, must not be confounded with that which succeeds the rise in animals where but small doses were injected. The former is due to paresis, or paralysis of the heart, while the latter, not occurring after section of the cervical pneumogastrics, is due to stimulation of these nerves.

*The action of saponin on arterial pressure when injected into an efferent blood-vessel.**

The injection of the drug into the internal carotid artery towards the brain.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
46.	Albino Rabbit.	Oct. 7, 1877.		Canula in carotid.
		10.22	52.4 mm.	
		10.22.30	52.4 "	
		10.23	52.4 "	
		10.24	52.2 "	
				.025 gram. into int'l carotid.
		.05	54. "	
		.10	56.2 "	
		.15	61. "	
		.20	64.1 "	
		.30	62.5 "	Clonic convulsions.
48.	Dog.	Nov. 7, 1877.		Canula in carotid.
		1 sec.	127.1 mm.	
		5 "		.1 gram. into internal carotid.
		10 "	138.8 "	
		15 "	144. "	
		20 "	149.4 "	
		30 "	157. "	
		120 "	104.6 "	

* The veins of the portal circulation are included under this head.

From these experiments it will be seen that saponin thus introduced, produces a rise in the arterial pressure, which rise in almost all my experiments was succeeded by a fall. The same effect was observed when the drug was injected into the portal circulation.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
49.	Large Rabbit.	Dec. 6, 1877.		Canula in carotid.
		1 sec.	82.8 mm.	
		5 "		.05 gram. into mesenteric vein.
		10 "	86.5 "	
		13 "	86.8 "	
		15 "	82.1 "	
		17 "	64.9 "	
		30 "	61.6 "	

An injection into a femoral artery is followed by the same effect.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
50.	Dog.	Dec. 13, 1877.		Canula in carotid.
		1 sec.	152.7 mm.	
		5 "		.2 gram. into femoral artery
		10 "	165.3 "	
		20 "	171.2 "	
		30 "	175.9 "	
		60 "	172.8 "	
		120 "	144.1 "	

That the rise in the blood-pressure produced in the above experiments was not due to paralysis of the pneumogastrics was determined by previously cutting these nerves, and then

injecting the drug as before, when a rise in the pressure still occurred. The secondary fall in the pressure, however, fails to occur in animals thus prepared.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
51.	Cat.	Nov. 30, 1877.		Canula in carotid. Vagi cut.
		1 sec.	110–113 mm.	
		5 "		.2 gram. into intl. carotid.
		10 "	130–136 "	
		15 "	132–138 "	
		20 "	150–154 "	
		30 "	149–153 "	
		55 "	142–145 "	
		120 "	110–113 "	

If the rise in the blood-pressure fails to occur when the spinal cord is cut in the upper dorsal or cervical regions, it must be due to vaso-motor stimulation.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
52.	Dog.	Dec. 20, 1877.		Section of medulla at calamus. Canula in carotid. Vagi cut.
		1 sec.	115–125 mm.	
				.1 gram. into femoral artery.
		10 "	115–125 "	
		15 "	115–125 "	
		30 "	115–125 "	
		60 "		.1 gram. into femoral artery.
		70 "	115–125 "	
		80 "	115–125 "	
		120 "	115–125 "	

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
53.	Dog.	Dec. 21, 1877.		Spinal cord cut at twelfth dorsal vertebra. Canula in carotid.
		1 sec.	119–121 mm.	
		5 "	119–121 "	.1 gram. into a mesenteric vein.
		10 "	119–121 "	
		15 "	119–121 "	
		30 "	119–121 "	
		60 "	119–121 "	
		70 "		.1 gram. into femoral artery.
		80 "	119–121 "	
		90 "	119–121 "	
		2 min.	119–121 "	
		2.30		.1 gram. into artery of thorax.
		.35	125–130 "	
		.40	140–145 "	
		.45	162–164 "	Tetanus.
		3.		Section at calamus; tetanus immediately ceased.
		3.20	98.2 mm.	
		.30		.1 gram. into artery of thorax.
		.34	98.2 "	
		.50	98.2 "	
		4.	98.2 "	
		5.	98.2 "	
		7.	98.2 "	

From these and other similar experiments, I arrived at the conclusion: that, the increase in the arterial pressure from an injection of saponin into an efferent blood-vessel does not occur if the spinal cord is cut high up, and consequently it

must be due to stimulation of the vaso-motor "centre." This "centre" may be stimulated either directly by the drug itself or reflexly from the action of the drug on the peripheral ends of the afferent nerve fibres. Were it due to the latter it is very apparent that if the connection of the sensory nerves of one posterior extremity with the spinal cord and brain is destroyed, and an injection made into an artery of that limb, the increased blood-pressure would not occur. If in the same animal, however, the drug was introduced into an artery of another extremity where the nerves were uncut, the rise in the pressure would still occur, provided it were due to a reflex stimulation of the vaso-motor "centre."

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
54.	Dog.	Dec. 6, 1877.		Canula in right femoral artery. Sciatic and anterior crural nerves cut on right side.
		1 sec.	107.5 mm.	
		3 "		.1 gram. into right femoral artery.
		7 "	107.5 "	
		14 "	104.1 112.4	
		30 "	107.5 mm.	
		40 "	107.5 "	
		60 "	107.5 "	
		120 "	107.5 "	
		4 min.		.1 gram. into right femoral artery.
		4.10 sec.	107.4 "	
		.20 "	107.6 "	
		.30 "	107.4 "	
		.40 "	107.5 "	
		.60 "	107.6 "	
		10 min.		.1 gram. into left femoral artery.
		.10 sec.	107.5 "	
		.20 "	111.6 "	
		.40 "	117.5 "	
		.60 "	112.1 "	
		11.40 "	101.4 "	
		23 m.	105.4 "	.1 gram. into left femoral artery.
		.10 "	109.6 "	
		.30 "	107.3 "	
		.50 "	108. "	
		28 m.	106.6 "	.1 gram. into right femoral artery.
		.10 "	106.6 "	
		.20 "	106.6 "	
		.30 "	106.6 "	
		29 m.	106.6 "	

A large number of similar experiments gave results identical with the above.

As was before shown (Experiments 46, 48 and 51,) an injection into the carotid artery towards the brain produces the same augmentation in blood-pressure. It was necessary to determine whether this augmentation was due to the direct effect of the drug on the vaso-motor "centres," or to an effect on fibres of the cerebrum, afferent to, and regulating the action of, this "centre." To do this a complete section of the pons was made and a canula placed in the femoral or carotid artery. If saponin was now injected into the carotid artery no effect on pressure occurred, though the usual result was observed when the drug was injected into a femoral artery.

No. of Experiment.	Animal.	Time.	Pressure.	REMARKS.
55.	Cat.	Dec. 16, 1877.		Section of pons. Canula in carotid.
		1 sec.	92.7 mm.	
		3 "		.1 gram. into carotid artery.
		10 "	92.7 "	
		15 "	92.7 "	
		18 "	92.6 "	
		30 "	92.7 "	
		40 "	92.7 "	
		60 "	92.7 "	
		3 min.	92.7 "	.1 gram. into right femoral artery.
		10 sec.	98.3 "	
		20 "	103.4 "	
		30 "	107.6 "	
		4 min.	104.2 "	
		6 "	87.4 "	
		7 "	92.7 "	Cut sciatic and anterior crural nerves on right side.
		10 min	92.6 "	.1 gram. into right femoral artery.
		10 sec.	92.6 "	
		20 "	92.6 "	
		40 "	92.6 "	
		11 min.	92.6 "	

The irritative effect of a saponin solution on the fibres of the cerebrum, which are afferent to the vaso-motor "centre," far exceeds that which is brought about by applying a strong induction current to the anterior crural nerve. In dogs, where the medulla oblongata and pons were so mutilated that strong irritations of the sciatic nerves failed to produce any change in the blood-pressure, a solution of saponin introduced into the internal carotid artery immediately occasioned a decided rise in the mercury of the manometer.

CONCLUSIONS.

1. *Saponin directly introduced into the jugular vein of a small mammal, or into the heart of a large animal, produces immediate cardiac paresis, and consequently a diminished arterial pressure.*
2. *The same dose of this drug injected into the femoral vein or an efferent blood-vessel produces: first, an augmented, followed by a diminished arterial pressure.*

The augmentation from the latter method, and probably also from the former, is due to the drug acting as an irritant to the afferent nerve fibres, and thereby, reflexly, stimulating the vaso-motor "centre."

The secondary fall in the blood-pressure produced by both these methods of introduction, is due to stimulation of the pneumogastric centres. This is also reflexly produced, because it does not occur if the afferent nerves of the limb into which the drug is, peripherally, introduced, are destroyed.

3. *Saponin is fatal in small doses when injected directly into the heart. It requires much larger doses to produce death when introduced into the femoral vein, and exceedingly large doses are required if the injection is made into an efferent blood-vessel.*

ACTION ON THE PULSE.

Bonneau and Malapert* found that when plants which owed their active properties to the presence of saponin were

* *Casper's Vierteljahrs. f. ger. u. öf. Medic.*, B. 2, Hft. 1, p. 101.

introduced into the alimentary canal of dogs, an increased frequency of the pulse was produced.

Hoppe* says that saponin first excites and then depresses the heart's action.

In frogs and rabbits, according to Köhler,† the pulse is slowed when this glucoside is introduced into the circulation.

Przybyszuoski‡ found saponin to slow the pulse.

The apparatus employed in my experiments on this subject was a Marey tambour, which was attached to the carotid, and made to write on a drum revolving at the rate of 60 cent. per minute.

An injection into the jugular vein of rabbits and cats, produces a marked diminution in the pulse-rate, which at the same time becomes very irregular.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
1.	Albino Rabbit.	Dec. 22, 1877.		Canula in carotid.
		3.14	96–200pm	
		.15		.05 gram. into jugular vein. Immediate cessation of heart beats, which soon recommenced.
		.17	148 "	
		.18	18 "	
		.20	0 "	Heart ceased to beat, but is still irritable.
3.	Large Cat.	Dec. 3, 1877.		Canula in carotid.
			123–120pm	
				.07 gram. into jugular vein.
			120 p.m.	
			114 "	
			107 "	
			118 "	
			120 "	
			123 "	

* *D. Nervenwirkung d. Arzneimittel*, II. IV., p. 137.

† *Arch. f. exp. Path.*, B. 1., p. 138-162.

‡ *Arch. f. exp. Path.*, B. 5, p. 137.

That this diminished frequency of the heart's action is not due to an effect on the nervous centres or pneumogastric nerves was shown in experiments where I destroyed these and then injected the drug.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
4.	Rabbit.	Nov. 19, 1877.		Canula in carotid. Vagi cut.
		1 sec.	6 in 1 sec.	
				.02 gram. into jugular vein.
		10 "	4½ " "	
		14 "	4½ " "	
		17 "	4¼ " "	
		24 "	4 " "	
7.	Cat.	Nov. 24, 1877.		Canula in carotid. Vagi cut.
		1 sec.	12 in 2 sec.	
				.015 gram. into jugular vein.
		10 "	12 " "	
		16 "	9 " "	
		60 "	10 " "	

The same effect was observed when saponin was applied to, or injected into the heart of frogs, in whom the central-nervous system had been destroyed.*

The diminished frequency of the pulse, under these circumstances, occurring independent of the vagus and brain, must be the result of an intra-cardiac action of the drug. If it be cardiac, there remains still to determine whether it be due to an effect on the heart muscle itself, or on the nerves and ganglia of this organ. Were the cardiac ganglia possessed of automatism, as is claimed by the majority of modern physiologists, the explanation would readily be found in supposing saponin to diminish their activity. This explanation would

* See, Local action on the heart.

be greatly assisted, if not confirmed, by the frequent persistence of cardiac irritability after cessation of the heart's beat. But as these ganglia have by no means been *proven* to be the cause of the movements of the heart, it would not be proper to conclude that a drug influences them either as a paretic or as an inhibitant. The only conclusion which can with certainty be drawn, is that the diminished frequency of the pulse following an injection of saponin into the jugular vein (*i. e.*, the heart), is due to a paretic action on the intrinsic structures of this muscle whose function it is to cause the heart to continue to beat after it is removed from the body of an animal.

When the drug is introduced into an afferent blood-vessel at some distance from the heart, or into an efferent blood-vessel, an increased followed by a decreased frequency of the pulse occurs.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
11.	Rabbit.	Feb. 12, 1878.		
			29 in 10 s.	
			29 " "	
			28 " "	
				.02 gram. into femoral vein
			33 " "	
			35 " "	
			25 " "	
			22 " "	
16.	Dog.	Dec. 12, 1877.		Canula in femoral artery.
		1 sec.	5 in 2 sec.	
				.125 gram. into femoral vein.
		12 "	6 " "	
		20 "	6¼ " "	
		40 "	6¼ " "	
		5 min.	4¼ " "	

An increased pulse-frequency, following the introduction of a drug at some distance from the heart, may be caused: first, by a cessation or diminution of the cardio-inhibitory action of the pneumogastrics; second, by a stimulation of any or all the nerves concerned in accelerating the heart's beat;* third, by a stimulation of the heart itself.

First, is the accelerated heart's action due to a diminished cardio-inhibitory action of the pneumogastrics?

It is well known that irritation of the neck pneumogastrics either arrests, or diminishes the number of heart beats, and if these nerves are paralyzed the heart beats are more frequent. To determine whether saponin paralyzes these nerves, two series of experiments had to be made: first, to determine whether in a poisoned animal irritation of the neck vagi still produces cardiac inhibition; second, whether after section of the pneumogastrics the glucoside still causes the heart's beat to increase in frequency.

Is the cardio-inhibitory-action on the heart lost?

Experiment 19. Cat. Vagi cut and electrodes from a Du-Bois Reymond induction apparatus (Leclanche cell) applied to them. Pulse 40-44 in 10 seconds. Irritation of vagi: Pulse ceases. Cessation of irritation, 48, 46, 42 in 10 seconds. Injected .075 gram. of saponin into femoral vein. Pulse, 50-54 in 10 seconds. Irritation of vagi: Pulse, 58 in 10 seconds. Cessation of irritation. Pulse, 59, 52, 49. Irritation of vagi: Pulse, 62 in 10 seconds.

Experiment 21. Rabbit. Prepared as above. Pulse, 28 in 10 seconds. Injected .15 gram. saponin into femoral artery. Pulse, 31 in 10 seconds. Irritation of vagi: Pulse, 35, 36, 38 in 10 seconds, Cessation of irritation. Pulse, 25, 28, 33.

Experiment 22. Dog. Prepared as in other experiments. Injected .25 gram. into the carotid artery. Pulse 11½ to 12 in 10 seconds. Irritation of vagi: Pulse, 15¾, 17¾, 18 in 10 seconds. Cessation of irritation. Pulse, 13, 15 in 10 seconds. Irritation of vagi: Pulse, 18, 19⅛ in 10 seconds. Cessation of irritation. Pulse, 15, 14 in 10 seconds.

* It has been contended that the blood-pressure mechanically influences the frequency of the pulse, but recent experiments have shown that this influence is only exerted indirectly through the heart-nerves.

From the above experiments it will be seen that, after an injection of saponin, irritation of the neck-pneumogastrics not only fails to produce heart-arrest, but on the contrary, causes cardiac excitation.* This shows that these nerves contained heart-accelerating as well as heart-inhibiting fibres. These experiments, however, do not necessarily prove that the inhibitory nerves are paralyzed, as it is possible that they remain unaffected while the excitability of the accelerating heart fibres of the pneumogastrics was increased by saponin.

As no other direct cardiac inhibitor is known to exist, I in a number of experiments cut the pneumogastrics and then gave the poison as before. If now the frequency of the pulse still increases, this result cannot be due to paralysis of these nerves.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
23.	Rabbit.	Jan. 2, 1878.		Cut vagi in the neck.
			17 in 10 s.	
		1.58		.02 gram. into femoral vein.
		.15	21 " "	
		1.59	20 " "	
		.30	18 " "	
		2.00	15 " "	
		2.01	15 " "	
25.	Dog.	Dec. 8, 1878.		Pneumogastric, sympathetic and recurrent nerves cut in the neck.
			3⅓ in 2 s.	
				.1 gram. into femoral vein.
		15 sec.	6 "	
		25 "	6 "	
		30 "	6 "	
		35 "	3⅛ "	
		60 "	2⅞ "	

* That the pneumogastrics contain accelerator nerves of the heart has frequently been shown by Moleschott, Schiff, Schmiedeberg, and others. After an injection of saponin, irritation of the vagi also produces a rise instead of a fall in the blood-pressure.

From a large number of experiments, similar to the above, I was led to the conclusion that neither the acceleration nor the diminution of the heart's beat was produced by any action on the pneumogastrics, neck sympathetic or recurrent laryngeal * nerves.

The only other nerves which have been asserted by physiologists to contain cardiac accelerators are the spinal branches of the ganglion stellatum of the sympathetic nerve. In order to determine whether or not the excitation of these nerves through saponin caused the increased frequency of the pulse, it was necessary to cut the spinal cord above their origin and then examine the effects of the poison.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
28.	Dog.	Dec. 14, 1877.		Spinal cord cut at fifth cervical vertebra. Vagi cut.
			6–6½ in 2 s.	
				.1 gram. into femoral vein.
		10 sec.	6½ "	
		20 "	6½ "	
		30 "	6 "	
		40 "	6 "	
		50 "	6 "	
		60 "	6 "	
		2 min.	6 "	
		3 "	6 "	
		5 "	32 in 10 s.	
29.	Cat.	Dec. 6, 1877.		Cord cut at fifth cervical vertebra.
			23 in 10 s.	
				.1 gram. into femoral vein.
		10 sec.	23 "	
		20 "	24 "	
		30 "	23 "	
		40 "	22 "	
		2 min.	22 "	
		5 "	22 "	

* That the recurrent laryngeal nerves contain heart accelerators has been abundantly demonstrated by the experiments of Schiff (*Altes u. Neues ueb. Herznerven*, etc.).

The acceleration of the heart's beat not occurring after section of the spinal cord above the origin of the spinal cardiac accelerators, it very likely is due to stimulation of these fibres or their centres. As the secondarily produced diminished frequency of the pulse also fails to be present after this operation, the conclusion must be drawn that this is due to a secondary paretic effect on these nerves or their centres. These centres must exist in the central nervous system below the pons, as it was found that, after complete section of the pons, an injection of saponin into the femoral vein still produces its characteristic effect on the pulse.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
30.	Dog.	Dec. 29, 1877.		Section of pons and vagi.
			20 in 10 s.	
				.1 gram. into femoral vein.
			35 " "	
			37 " "	
			38 " "	
			38 " "	
			38 " "	
		5 min.	16 " "	

The primary excitation and the secondary paresis of these nerves must be produced reflexly through stimulation of afferent nerves; for if the afferent nerves of a limb are cut, and saponin is injected into its artery, they fail to occur, though the rest of the nervous system be normal. This is an interesting physiological phenomenon, the possibility of which has never before been demonstrated.

No. of Experiment.	Animal.	Time.	Pulse.	REMARKS.
32.	Dog.	Dec. 18, 1877.		Canula in femoral artery. Sciatic and anterior crural nerves cut on the right side.
			6½–6¾ in 2s.	
				.1 gram. into right femoral artery.
		7 sec.	6¾ "	
		14 "	6¾ "	
		40 "	6¾ "	
		60 "	6½ "	
		4 min.	6¾ "	
				.1 gram. into right femoral artery.
		20 "	6¾ "	
		40 "	6½ "	
		5 min.		.1 gram. into left femoral artery. On this side the nerves were intact.
		10 "	7 "	
		20 "	8¾ "	
		30 "	8½ "	
		40 "	8 "	
		50 "	8 "	
		6 min.	2⅓ in 5s.	
		10 "	5 "	
		40 "	2⅓ "	
		11 min.	5½ "	
		40 "	6 "	
		23 min.	5¾ "	.1 gram. into left femoral artery.
		10 "	6¼ "	
		40 "	7¾ "	
		50 min.	3¾ "	

CONCLUSIONS.

1. *Saponin directly introduced into the heart diminishes the frequency of the pulse through its paretic effect on the excito-motor mechanisms of this muscle.*

2. *Introduced into a vein at some distance from the heart, or into an efferent blood-vessel, it reflexly excites the accelerators of the heart which exist in the cervical spinal cord. The excitation is followed by paresis of these nerves. Both the paresis and the excitation are due to the action of the drug on the afferent nerve fibres.*

ACTION ON THE RESPIRATORY SYSTEM.

The local action of saponin on the mucous membrane of the air passages was treated of on one of the earlier pages of this work. Introduced anywhere into a living animal it produces an increased mucous discharge from the bronchial tubes. How it produces such an increased secretion I shall here endeavor to explain.

A well known fact in the physiology of secretion is, that an increased elimination from a secreting surface must be due to an increased blood-supply to its secreting apparatus. So it is with the lungs: saponin introduced into the stomach, into the blood-vessels, or endermically, invariably produces hyperæmia of the lungs. This, it may be contended, is only a collecting of the blood in the radicles of the pulmonary vein. Careful examination has, however, convinced me that not only do the pulmonary vessels contain more blood than normally, under these circumstances, but the bronchial vessels are also surcharged with this fluid. Even going aside from these observations, anatomists have shown that communications exist in the lungs between the bronchial and pulmonary vessels. So that if one set of vessels be surcharged with blood the other set must be similarly affected. *The increase in the bronchial discharge must therefore be due to the increased vascularity of the lungs* which follows the introduction of this drug.

To what is the increased vascularity due?

Hyperæmia of the lungs may be caused by contraction of the left auriculo-ventricular valve impeding the outflow of the

blood from the left auricle, and also by insufficience of this valve with systolic regurgitation from ventricle to auricle, and as a consequence the left auricle and pulmonary vein can empty their contents only with great difficulty. Under these circumstances, according to Niemeyer,* "Bronchial catarrh is not only one of the most constant, but one of the most physiological and inevitable symptoms." As, however, saponin does not produce "heart murmurs" of any kind, these causes may be excluded.

The only other known cause to account for the hyperæmia of the lungs is, paralysis of the vaso-motor nerves of these organs. On examining the various monographs on the vaso-motor nerves, I have been struck with the utter lack of allusion to the vascular nerves of the lungs, so that on commencing the experiments on the respiratory action of saponin I was compelled to precede them by other experiments to determine which were these nerves.

The vascular nerves of the lungs certainly do not arise from the spinal cord, as section of this at any point below the medulla oblongata is followed by anæmia instead of hyperæmia of the lungs. The only other nerves which directly supply these organs are the pneumogastrics, section of which has been known since the beginning of the present century to produce an increased vascularization of the lungs. So that it seems very probable that vaso-motor nerves for the lungs exist in these nerves, an inference which my experiments on saponin have confirmed.

When the hyperæmia has been produced by the drug, irritation of the cervical pneumogastric trunks causes the hyperæmia to disappear immediately, to reappear again on removing the irritation. This experiment was repeatedly made with unvarying results. This effect of the pneumogastrics on the vascular supply of the lungs is not due to inhibition of the heart, as in saponized animals irritation can no longer produce inhibition. *The cause of the increased vascularity of the lungs is very probably to be found in a paresis of the respiratory vascular nerves.*

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* *Practical Medicine*, Am. Ed., V. 1, p. 60.

Saponin also affects the respiratory movements, making them irregular in rhythm and usually more frequent.

Experiment on a rabbit. Respirations, 60 per min.

11.53. Injected .01 gram. into femoral vein.

11.56½. Respirations, 67 per minute.

11.59. " 64 "

12.02½. " 64 "

12.04. " 66 "

12.12. " 64 "

12.24. " 66 "

Experiment on a dog. Respirations, 9 per minute.

9.56. .1 gram. of saponin into femoral vein.

9.56½. Respirations, 12 per minute.

9.58. " 18 "

Though in these and other similar experiments a decided increase in the number of respiratory movements occurred, in quite a number of other experiments the opposite result was obtained. When, however, the cervical pneumogastrics were previously cut, an injection of saponin almost always produced a diminution in the number of respiratory movements, showing that the opposite effect on animals in whom these nerves have not been cut, is very probably produced by irritation of the afferent pneumogastric fibres in the lungs.

The usual effect in non-poisoned animals of irritation of the peripheral extremities of the cut cervical pneumogastrics is to decrease the number of respiratory movements; but after an injection of saponin irritation of these nerves increases the number of these movements.

Experiment on a cat. Vagi cut. Respirations, 12 per minute. Irritation of vagi: Respirations, 10 per minute.

Injected .1 gram. saponin into the femoral vein. 3 minutes after the injection: respirations 9 per minute. Irritation of the peripheral ends of the cut vagi increase their number to 12 per minute.

ACTION ON THE SECRETORY ORGANS.

A solution of the drug introduced into the general circulation apparently does not affect the secretions from the salivary, biliary, and renal glands. Through the aid of

fistulas it was determined that no change in the amount secreted took place from any of these glands. With the gastric juice the result was different, its secretion was increased.

The local irritant effects of saponin on the stomach in producing vomiting, etc., have already been noticed. Vomiting is, however, also produced when this drug is introduced into the general circulation. This symptom may be produced by an action on the vomiting "centre" in the medulla oblongata; it may be reflex: or it may be of gastric origin. If it be the latter, saponin must be eliminated by the stomach. I have found in a number of experiments that while the normal gastric juice contains no substance which reacts like our glucoside, yet 15–30 minutes after the injection of a solution of the latter into a vein, or several hours after its introduction endermically, saponin can be detected in the secretion of the stomach. In the matters vomited by these animals traces of it were also found. It appears from this that *the vomiting produced by this drug is always of gastric origin.*

The peristaltic movements of the intestines are much increased by saponin. This effect may be due to paralysis of the inhibitory fibres (splanchnici) of these structures, or to a stimulation of their excito-motor nerves (pneumogastrics?).

Pflüger* found that irritation of the splanchnic nerves produced peristaltic inhibition. If the increased peristalsis from saponin was due to paralysis of these nerves, their irritation would no longer inhibit these movements. But as their irritation still inhibited the peristaltic movements, *the increased peristalsis from saponin must have been due to stimulation of the excito-motor nerves of these viscera.*

ABSORPTION AND ELIMINATION.

That saponin is absorbed is beyond doubt, as its general effects are manifest even when it is introduced into the stomach or endermically. That it is eliminated as saponin by the stomach and liver was proven by numerous experiments. The secretions from these organs invariably reacting for the gluco-

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* *Ueb. Hemmungsnervensystem f. d. peristal. Beweg. d. Gedarme.* Berlin, 1857.

side after its introduction into the general circulation, but do not affect the re-agents normally.

Whether the drug is eliminated by the urine could not be determined, as the presence of the phosphates and sulphates too greatly interfered with the tests.

Is saponin destroyed by the liver? This was a very difficult question to answer, but after making a large number of experiments, I am now able to say that the drug is not destroyed, but is eliminated by the liver.

The circumstance that saponin is poisonous in smaller doses when introduced into the jugular vein, than when it is injected into the portal circulation, does not aid us here, as by the former method we have the direct effect on the heart which so rapidly kills the animals experimented upon. Saponin is also less poisonous if injected into the femoral artery, than if it was introduced into the portal circulation.*

In the frog experiments more positive results were obtained; but even these, as will be seen later, only demonstrate that the liver eliminates the poison. The drug used was poisonous to medium-sized frogs in doses of .0035 gram., while doses of .0023 gram. failed to produce fatal results.

When, however, the livers of these animals were removed, the last mentioned dose invariably proved fatal.

Aug. 30, 1877. Experiment on a medium-sized frog. Extirpated the liver. 1.23. Injected .0023 gram. of saponin into the lymph sac of the back. This dose produced no symptoms previous to the removal of liver. 2.00. Voluntary and reflex movements have ceased. 2.10. The circulation in the capillaries of the web of the foot has ceased. Muscles and nerves are still irritable.

Aug. 25, 1877. Experiment on a medium-sized frog (*R. esculenta*). 10.30 A. M. Injected .0023 gram. into lymph sac of back. No symptoms were produced.

Aug. 31, 1877. Extirpated the liver of a large female frog (*R. temporaria*) at 2.48 P. M.

Sept. 1, 11 A. M. Animal is as well as ever and very lively.

11.01. .0023 gram. saponin into back.

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* Nicotine gives somewhat similar results.

11.45. The animal moves with great difficulty.

4. P. M. Tetanus, no voluntary movements.

4.35. Reflex movements have ceased.

Though large numbers of similar experiments were made, the above will suffice to show that the presence or absence of the liver greatly influences the dose of saponin necessary to kill such an animal. This however does not prove its destruction by the liver. If the poison be eliminated by this organ, as has been proven, it is very apparent that its removal will cause a greater amount of the poison to remain in the system. As a consequence the effects of saponin are greater in liverless than in normal animals.

To determine beyond a doubt, whether the drug is or is not destroyed by the liver, it was necessary to tie the gall-ducts of a frog, and then observe the effects of a dose of the poison which under ordinary circumstances would not kill the animal. If this be done the liver is still able to destroy the drug though it is unable to eliminate it.

Sept. 3, 1877. Experiment on a large frog (*R. esculenta*).

9.45 A. M. Ligated gall-bladder and bile-ducts.

11 A. M. No symptoms.

11.10 A. M. Injected .0023 gram. saponin into back.

12 M. Voluntary and reflex movements are almost abolished.

1.27 P. M. The animal is dead.

Sept. 4, 1877. Experiment on a medium sized frog (*R. esculenta*).

9.08 A. M. Injected .0023 gram. into back.

11.23 A. M. No symptoms.

1 P. M. No symptoms.

4 P. M. No symptoms have occurred.

Sept. 5, 1877, 10.31 A. M. Ligated gall-ducts.

11.17 A. M. Injected .0023 gram. into back.

By 1.30 P. M. the frog was dead.

From these experiments it appears that saponin is not destroyed but is eliminated by the liver. The fact, previously mentioned, that when a mammal dies from saponin-poisoning the presence of the poison can be detected in the bile, goes to confirm this. To still further test the correctness of this re-

sult I rendered the liver hyperæmic, after the beautiful method of Schiff, by tying the superior vena cava. If saponin is removed by the liver a greater quantity will be eliminated when this vein is tied, forcing all the blood from the abdomen and lower extremities through this organ. In a number of frogs I made this operation, and then injected poisonous doses of the drug without producing fatal results.

Sept. 3, 1877, 10.30 A. M. Ligated the superior vena cava of a medium-sized frog.

12.27 P. M. Injected .004 gram into back.
12.47 P. M. No symptoms.
1.00 " " "
2.02 " " "
2.30 " " "
3.00 " " "
3.15 " " "
3.30 " " "

Sept. 4, 10.15 A. M. As yesterday, with the exception of an inclination to keep quiet.

From the above given facts the conclusion must be drawn that *saponin is eliminated and not destroyed by the liver.*

EXPERIMENTS ON THE CHEMISTRY OF VARIOUS PLANTS CONTAINING SAPONIN.

Saponin, as was stated on one of the early pages of this work, is contained in a large number of plants. My investigations were made on the *Saponaria officinalis*, *Quillaya saponaria*, and *Polygala senega*. All these contain, besides saponin, kino-tannic acid. This can be extracted from the filtered watery extract of the drugs, by means of ether, and also by maceration with ether and then filtering. By either of these methods quite an appreciable quantity of saponin was extracted with the acid, as was determined by the physiological, as well as by the chemical tests. For these tests the ethereal solution was evaporated over a sand bath and the residue was dissolved in water. This solution was now treated with boiling alcohol, which precipitated the glucoside. A watery solution of this precipitate reacted in every way for saponin;—a precipitate was given with soluble lead and barium salts;

blood-corpuscles were dissolved by it; and injected into the jugular vein of a rabbit, it produced cardiac paralysis.

After ether has extracted all possible from the drugs investigated, water is allowed to percolate through the residue, when an acid filtrate is obtained. The acid of this filtrate did not react with iron salts, and consequently was neither kino- nor gallo-tannic acid. On evaporating this filtrate to dryness and treating it repeatedly with concentrated ether the acidity gradually disappeared, and only a neutral saponin in a pure state remained. More especially were my investigations directed to the root of the *Polygala senega*, from which Quevenne obtained an acid having the properties of saponin, which was called by him acid saponin or polygalic acid.

Saponin obtained from senega by precipitation from the extract by boiling alcohol is, as Quevenne says, of an acid reaction; but this saponin, after concentrated ether has been allowed to percolate through it for a long time, becomes neutral, though it still presents all the characteristics of the glucoside, showing that the acidity is due to the presence of a foreign acid and not to saponin.

Saponin in combination with sulphuric acid.—When to a solution of the glucoside dilute sulphuric acid is added and the resulting liquid is allowed to concentrate, after a time beautiful acicular prisms are found to shoot out at the edge of the liquid.* These crystals when burned leave but a faint trace of ash, showing that they are crystals of an organic compound. They are freely soluble in water; and when a drop of this solution is added to several drops of blood under the microscope, the corpuscles immediately disappear. Injected into a lymph sac of a frog it produces all the symptoms of saponin poisoning.

Saponin is the only glucoside known to form compounds with an acid and at the same time retain its peculiar properties.

* I have several times seen very small rhombic crystals in a solution of neutral saponin.